REMARKS

Prior to entry of this Amendment, Claims 1, 3, 5-9, 12-15, 17 and 19 are pending in the application and Claims 6-8, 13 and 17 are withdrawn. Claims 1 and 15 are amended herein. Upon entry of this Amendment, Claims 1, 3, 5-9, 12-15, 17 and 19 remain pending. The claim amendments are supported in the specification, drawings, and claims as originally filed, including Paragraphs [0024] and [0028] of the specification as originally filed. Applicant submits that the claim amendments place the application in condition for allowance. The Examiner is respectfully requested to reconsider and withdraw the rejection(s) in view of the amendments and remarks contained herein.

REJECTION UNDER 35 U.S.C. § 112

Claims 12, 15 and 19 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Claim 12 has been amended to remove the "such as" limitation. Claim 15 has been amended to recite "said defect." Withdrawal of the rejection is requested as the rejection should now be moot.

REJECTION UNDER 35 U.S.C. § 103

Claims 1, 3, 5, 9, 12, 14, 15 and 19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent. No. 6,372,494, Naughton et al., issued April 16, 2002 (hereinafter referred to as "*Naughton*") in view of U.S. Patent No. 6,228,580, Jaggi et al. issued May 8, 2001 (hereinafter referred to as "*Jaggi*"), and in view of U.S. Patent No. 5,195,940, Baylink, issued March 23, 1993 (hereinafter referred to as "*Baylink*") and/or U.S. Patent No. 6,334,069, George et

al., issued December 25, 2001 (hereinafter referred to as "*George*"), and/or U.S. Patent No. 7,089,060, Fitzsimmons, issued August 8, 2006 (hereinafter referred to as "*Fitzsimmons*"), and/or PCT Publication No. WO2000027466, Conrad-Vlasak et al., published May 18, 2000 (hereinafter referred to as "*Conrad-Vlasak*").

Claims 1, 3, 5, 9, 12, 14, 15 and 19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Marchosky et al. (WO 01/00792) (hereinafter referred to as "*Marchosky*") in light of *Jaggi*, and in view of *Baylink*, *George*, *Fitzsimmons*, and *Conrad-Vlasak*.

These rejections are respectfully traversed.

Claims 1 and 15 as amended recite that the endothelial cell tissue culture is subjected to a pulsed electromagnetic field in vitro for at least about 8 hours delivered at about 4.5 seconds pulses at about 15 Hertz.

Naughton describes the use of conditioned cell medium from stromal cells, which include endothelial cells. The conditioned medium contains growth factors and the cell conditioned medium are said to be used to treat, repair or regenerate tissue defects. The conditioned medium described is also said to be used to stimulate angiogenesis and induce cell proliferation because the conditioned medium comprises angiogenic growth factors such as vascular endothelial growth factor (VEGF) and other cell growth factors.

Marchosky describes the use of a composition comprising the following components: (a) one or more angiogenesis-stimulating materials; (b) an osteoinductive material; (c) a scaffolding material; and (d) a gel material. Pg. 8, ll. 20-28. *Marchosky* alleges when this composition is placed in a location where bone growth is desired, the composition components work together. Pg. 9, ll. 1-4. *Marchosky* does not disclose a method of treating a bone or cartilage tissue defect comprising

culturing endothelial cells in a tissue culture medium to form an endothelial cell tissue culture and subjecting the endothelial cell tissue culture to a pulsed electromagnetic field in vitro. Further, *Marchosky* does not teach or suggest extracting the tissue culture medium from the endothelial cell tissue culture and administering the tissue culture medium to the site of the bone or cartilage tissue defect.

Naughton and *Marchosky* are acknowledged in the Office Action as differing from the present invention because they fail to disclose the use of pulsed electromagnetic fields (PEMF) to prepare the cell culture medium. To remedy this deficiency in *Naughton* and *Marchosky*, the Office Action relies on *Jaggi*, in view of *Baylink*, *George* and *Fitzsimmons* as teaching the production of growth factor from living tissue including in vitro cell cultures using PEMF.

Jaggi is alleged to teach that during angiogenesis, endothelial cells proliferate. (See Office Action pgs. 5 and 8.) *Jaggi* discloses the use of betulinc acid and/or derivatives for inhibiting and/or preventing angiogenesis. Abstract and Col. 4, ll. 31-34. Thus, *Jaggi* actually teaches away from enhancing proliferation of endothelial cells and stimulating angiogenesis.

Reliance on *Baylink*, *George* and *Fitzsimmons* is also misplaced. First, *Baylink* discloses cell proliferation of cells other than endothelial cells, human osteosarcoma cells (TE-85). Furthermore, *Baylink* teaches or suggests exposing the TE-85 cells to a magnetic field that consists of a 200 milligauss dc component and a 400 milligauss ac component oscillating at 15.3 Hertz (sine wave) for about 30 minutes.

Second, *George* discloses cell proliferation of cells other than endothelial cells, specifically Rat-2 immortalized and SA-1 human primary fibroblasts cell lines. The cells described in *George*

are exposed to radio frequency electromagnetic energy in doses from 600-1500 pulses per second and the timer is set between about 16-60 microseconds. Col. 12, ll. 41-52.

Finally, *Fitzsimmons* discloses a method for activating a vascular endothelial growth factor (VEGF) in MG-63 osteosacroma cell lines. *Fitzsimmons* teaches or suggests exposing the MG-63 cells to PEMF to a burst that includes multiple phases. Col. 5, ll. 39-40. For example, *Fitzsimmons* discloses using PEMF for a pulse period for 4μ seconds at 62,500 Hertz for 16μ seconds or 65μ seconds at 3831 Hertz for 196μ seconds. Col. 5, ll. 47-48 and Col. 6, ll. 5-12. However, neither *Baylink*, *George* nor *Fitzsimmons* teach or suggest culturing endothelial cells in a tissue culture medium to form an endothelial cell tissue culture and subjecting the endothelial cell tissue culture to a pulsed electromagnetic field in vitro for at least about 8 hours delivered at about 4.5 seconds pulses at about 15 Hertz, as stated in the amended claims.

The Office Action recognizes that *Naughton*, *Marchosky*, *Baylink*, *George* and *Fitzsimmons* all fail to teach application of PEMF for at least 8 hours. To remedy this deficiency, the Office Action relies on *Conrad-Vlasak*. *Conrad-Vlasak* describes a method of treatment using living cells that have been removed from the patient and stimulated with an electrical field to increase vascular endothelial growth factor (VEGF). Pg. 5, ll. 19- 23. The stimulated cells are then injected into the targeted body tissue. Pg. 6, l. 3. *Conrad-Vlasak* describes producing the electrical stimulation in a range of 1 to about 1000 pulses with a frequency between 0.1 Hz to about 5 Hz for a duration between about 0.0001 to several days. *Conrad-Vlasak* fails to teach or suggest a method of treating defect comprising culturing endothelial cells in a tissue culture medium to form an endothelial cell tissue culture and subjecting the endothelial cell tissue culture to a pulsed electromagnetic field in

vitro for at least about 8 hours delivered at about 4.5 seconds pulses at about 15 Hertz, as stated in the amended claims.

The Office Action assumes that applying PEMF to the co-cultures in *Naughton* and *Marchosky* would have resulted in a tissue culture media that is capable of enhancing proliferation of endothelial cells. None of the cited references teach or suggest such a utility. Accordingly, Applicant requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

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Respectfully submitted,

By _____

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